Guideline for Industry

Dose-Response Information to Support Drug Registration

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TABLE OF CONTENTS

GUIDELINE FOR INDUSTRY[1]

DOSE-RESPONSE INFORMATION TO SUPPORT DRUG REGISTRATION

I. INTRODUCTION

A. Purpose of Dose-Response Information

Knowledge of the relationships among dose, drug concentration drug concentration in blood, and clinical response (effectiveness and undesirable effects) is important for the safe and effective use of drugs in individual patients. This information can help identify an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects. Dose-concentration, concentration- and/or dose-response information is used to prepare dosage and administration instructions in product labeling. In addition, knowledge of dose-response may provide an economical approach to global drug development, by enabling multiple regulatory agencies to make approval decisions from a common

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[1]This guideline was developed within the Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, March 10, 1994. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and the USA. This guideline was published in the Federal Register on November 9, 1994 (59 FR 55972) and is applicable to both drug and biological products. In the past, guidelines have generally been issued under § 10.90(b) [21 CFR 10.90(b)], which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but that are acceptable to FDA. The agency is now in the process of revising §10.90(b). Therefore, this guideline is not being issued under the authority of §10.90(b), and it does not create or confer any rights, privileges or benefits for or on any person, nor does it operate to bind FDA in any way. For additional copies of this guideline contact the Executive Secretariat Staff, HFD-8, Center for Drug Evaluation and Research, 7500 Standish Place, Rockville, MD, 20855, 301-594-1012. An electronic version of this guideline is also available via Internet by connecting to the CDER FTP server (CDVS2.CDER.FDA.GOV) using the FTP protocol.

database.

Historically, drugs have often been initially marketed at what were later recognized as excessive doses (i.e., doses well onto the plateau of the dose-response curve for the desired effect), sometimes with adverse consequences (e.g., hypokalemia and other metabolic disturbances with thiazide-type diuretics in hypertension). This situation has been improved by attempts to find the smallest dose with a discernible useful effect or a maximum dose beyond which no further beneficial effect is seen, but practical study designs do not exist to allow for precise determination of these doses. Further, expanding knowledge indicates that the concepts of minimum effective dose and maximum useful dose do not adequately account for individual differences and do not allow a comparison, at various doses, of both beneficial and undesirable effects. Any given dose provides a mixture of desirable and undesirable effects, with no single dose necessarily optimal for all patients.

B. Use of Dose-Response Information in Choosing Doses

What is most helpful in choosing the starting dose of a drug is knowing the shape and location of the population (group) average dose-response curve for both desirable and undesirable effects. Selection of dose is best based on that information, together with a judgment about the relative importance of desirable and undesirable effects. For example, a relatively high starting dose (on or near the plateau of the effectiveness dose-response curve) might be recommended for a drug with a large demonstrated separation between its useful and undesirable dose ranges or where a rapidly evolving disease process demands rapid effective intervention. A high starting dose, however, might be a poor choice for a drug with a small demonstrated separation between its useful and undesirable dose ranges. In these cases, the recommended starting dose might best be a low dose exhibiting a clinically important effect in even a fraction of the patient population, with the intent to titrate the dose upwards as long as the drug is well tolerated. Choice of a starting dose might also be affected by potential intersubject variability in pharmacodynamic response to a given blood concentration level, or by anticipated intersubject pharmacokinetic differences, such as could arise from nonlinear kinetics, metabolic polymorphism, or a high potential for pharmacokinetic drug-drug interactions. In these cases, a lower starting dose would protect patients who obtain higher blood concentrations. It is entirely possible that different physicians and even different regulatory authorities, looking at the same data, would make different choices as to the appropriate starting doses, dose-titration steps, and maximum recommended dose, based on different perceptions of risk/benefit

relationships. Valid dose response data allow the use of such judgment.

In adjusting the dose in an individual patient after observing the response to an initial dose, what would be most helpful is knowledge of the shape of individual dose-response curves, which is usually not the same as the population (group) average dose-response curve. Study designs that allow estimation of individual dose-response curves could therefore be useful in guiding titration, although experience with such designs and their analysis is very limited.

In utilizing dose-response information, it is important to identify, to the extent possible, factors that lead to differences in pharmacokinetics of drugs among individuals, including demographic factors (e.g., age, gender, race), other diseases (e.g., renal or hepatic failure), diet, concurrent therapies, or individual characteristics (e.g., weight, body habitus, other drugs, metabolic differences).

C. Uses of Concentration-Response Data

Where a drug can be safely and effectively given only with blood concentration monitoring, the value of concentration-response information is obvious. In other cases, an established concentration-response relationship is often not needed, but may be useful: (1) For ascertaining the magnitude of the clinical consequences of pharmacokinetic differences, such as those due to drug-disease (e.g., renal failure) or drug-drug interactions; or (2) for assessing the effects of the altered pharmacokinetics of new dosage forms (e.g., controlled release formulation) or new dosage regimens without need for additional clinical trial data, where such assessment is permitted by regional regulations. Prospective randomized concentration-response studies are obviously critical to defining concentration monitoring therapeutic "windows," but are also useful when pharmacokinetic variability among patients is great; in that case, a concentration-response relationship may in principle be discerned in a prospective study with a smaller number of subjects than could the dose-response relationship in a standard dose-response study. Note that collection of concentration-response information does not imply that therapeutic blood level monitoring will be needed to administer the drug properly. Concentration-response relationships can be translated into dose-response information. Concentration-response information can also allow selection of doses (based on the range of concentrations they will achieve) most likely to lead to a satisfactory response. Alternatively, if the relationships between concentration and observed effects (e.g., an undesirable or desirable pharmacologic effect) are defined, the drug can be titrated according to patient response without the need for further

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